Research Article

Evaluation of the Effects of Drotaverine and *Nardostachys jatamansi* on Hypertension in Wistar Rats

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Received: 20-12-2024; **Revised:** 28-02-2025; **Accepted:** 09-03-2025; **Published online:** 20-03-2025.

ABSTRACT

Objectives: Hypertension is a significant public health issue in India, affecting 24% of men and 21% of women, with over 50% unaware of their condition. Obesity, diabetes, high salt intake, and sedentary lifestyles are the main causes of uncontrolled hypertension. To tackle this issue, we explore the effects of drotaverine and *Nardostachys jatamansi* on fructose induced hypertension in male Wistar rats with amlodipine as the standard drug.

Methods: This was an experimental study carried over a period of 10 weeks. A total of 42 rats were randomly divided into 7 groups with 6 rats in each group. Drinking water was replaced with 10% fructose solution in all groups except Group 1, and rats in Group 2 received no treatment. Drotaverine (8 and 25 mg/kg/d), *Nardostachys jatamansi* (200 and 300 mg/kg/d), and amlodipine (10 mg/kg/d) were administered to groups 3,4,5,6 and 7, respectively.

Results: Hypertension developed in the 6th week in all the groups except the control group. At the end of 10 weeks- SBP was significantly decreased in groups 3,4,5,6 and 7 as compared to group 2 ($p<0.001$), SBP of none of the treatment groups (3,4,5 and 6) was significantly different from the standard drug amlodipine and SBP of drotaverine groups and Jatamansi groups did not differ significantly from each other.

Conclusion: Both drotaverine and *Nardostachys jatamansi* showed antihypertensive effect in the present study.

Keywords: Drotaverine, *Nardostachys jatamansi*, Amlodipine, Fructose induced hypertension, Antihypertensive

INTRODUCTION

Hypertension is a major public health problem affecting about 26% of the population worldwide and is expected to rise in the near future. In India the prevalence of hypertension is 29.8%. Only 10% of the patients in rural and 20% in urban areas have their BP under control.[1]

Hypertension is defined as (i) elevated BP, with a systolic pressure (SBP) of >120 to 129 mm Hg and diastolic pressure (DBP) less than 80 mm Hg, (ii) stage 1 hypertension, with an SBP of 130 to 139 mm Hg or a DBP of 80 to 89 mm Hg and (iii) Stage 2 hypertension, with a SBP of 140 mm Hg or greater or a DBP of 90 mm Hg or greater. [2]

Several different drugs, such as Calcium Channel blockers(CCBs), Angiotensin-converting enzyme (ACE) inhibitors, Diuretics, Angiotensin II receptor blockers (ARBs) and Beta-blockers are available for the treatment of hypertension. ACE inhibitors, ARBs and CCBs mainly lower BP by causing vasodilation. Amlodipine, a commonly used CCB as first line agent in the treatment of hypertension is taken as the standard drug. [3]

These days there is an increasing tendency to consume fast foods. Fast foods often have high salt content leading to hypertension. Moreover, fast foods contain large amounts of fats which has been linked with the development of endothelial dysfunction which is implicated in the pathogenesis of hypertension. Thus, the co-morbidity of obesity and hypertension highlights the need for innovative treatment strategies. [4-9]

To tackle this issue, we looked for herbal treatments as alternatives. Traditional systems of medicine have long utilised Nardostachys jatamansi to treat a variety of diseases including hypertension. *Nardostachys jatamansi* is being used as an antihypertensive agent in both Ayurvedic and Unani systems of medicine. It is an erect perennial herb of 10-60 cm height found at an altitude of 3000-5000 m in the Himalayas. It has been shown to exhibit angiotensin-converting enzyme inhibitory activity in-vitro. Research indicates that it may help regulate blood pressure by relaxing blood vessels, lowering inflammation, and enhancing endothelial function. [10-13]

Another approach which we have explored is drug repurposing. It involves identifying existing drugs, which are already approved for other diseases, that might be effective against hypertension. Drotaverine is one such medication. It is a phosphodiesterase-4 inhibitor commonly used as an antispasmodic agent. It has shown L-type calcium channel blocking property in vitro as well as similarity with CCBs used for hypertension in computational studies. [14-15]

However, no studies have been done till now to validate the antihypertensive effect of drotaverine in vivo. Also, no studies could be identified after a comprehensive literature search directly comparing the effects of drotaverine and *Nardostachys jatamansi* on SBP in rats, with amlodipine as the standard drug.

Present study aims to evaluate the effect of drotaverine and *Nardostachys jatamansi* on systolic blood pressure in Wistar rats with amlodipine as the standard drug.

MATERIALS AND METHODS

This is a laboratory based study conducted in the department of Pharmacology at a medical college in Lucknow for a duration of 3 months.

Following materials were procured for the research work as follows:

1. Japtose's Crystal Fructose – 100% pure crystalline fructose manufactured by Nihal marketing, 1st floor, No.6/1, 2nd cross, Tulsi Thota Lane, Balepet, Bangalore.
2. Drotaverine – Drotin suspension 10mg/5mL, manufactured by Martin and Harris Laboratories Ltd., Haridwar, marketed by Walter Bushnell.
3. Jatamansi Capsule containing 500mg Jatamansi extract – manufactured by DAV Pharmacy, Mahatma Hans Raj Marg, GT Road, Jalandhar.
4. Amlodipine – Amlokind 5mg tablets, manufactured by Mankind Pharma.

After approval from the Institutional Animal Ethics Committee (**IAEC Approval No.** IAEC/Dr.RMLIMS/05/2022), a total of 42 Adult healthy Wistar rats of either sex, similar physical constitution in terms of age, body weight; weighing 150±10 g each were obtained from the institutional animal house. They were given standard laboratory diet and drinking fluid ad libitum and were kept in the institutional animal house on a 12-hour light/12-hour dark cycle at a temperature of 22±2 °C. Before the start of the study, rats were acclimatised for 1 week followed by habituation for blood pressure measurements daily for 1 week.

Drinking fluid was RO-water for the control group. To induce hypertension, drinking water was replaced with 10% fructose solution for all other groups.

The dose of Drotaverine and *Nardostachys jatamansi* was calculated as per the formula:

Animal dose = Human dose x $\frac{K(human)}{K(animal)}$

K(human) = 37 and K(rat) = 6. [16]

The dose (for an adult human of 60 kg) of Drotaverine is 80-240 mg per day and the dose of *Nardostachys jatamansi* as per Ayurvedic Pharmacopoeia of India is 2-3g per day [17-18]. So, the corresponding dose in rats is:

1. Drotaverine: 8 mg/kg and 25 mg/kg
2. *Nardostachys jatamansi*: 200 mg/kg and 300 mg/kg

Amlodipine was given in a dose of 10mg/kg as per the previous studies. [19-21]

The LD_{50} of drotaverine is 540 mg/kg. The LD_{50} of *Nardostachys jatamansi* after oral administration is >5000 mg/kg and a dose of 1000 mg/kg/d did not produce any toxicity in 28-day toxicity test. Thus, our calculated doses of both drotaverine and *Nardostachys jatamansi* are well within the safe limits. [22-23]

Study design:

A total of 42 rats were randomly divided into 7 groups with 6 rats in each group:

- **Group 1(C): Control group-** was given RO-water ad libitum.
- **Group 2(D): Disease group-** was given 10% fructose solution for 10 weeks.
- **Group 3(DR8):** was given 10% fructose solution and drotaverine (DR8) 8 mg/kg/d by oral gavage (from 7th to 10th week).
- **Group 4(DR25):** was given SLD, 10% fructose solution and drotaverine (DR25) 25 mg/kg/d by oral gavage (from 7th to 10th week).
- **Group 5(J200):** was given 10% fructose solution and *Nardostachys jatamansi* extract (J200) 200 mg/kg/d by oral gavage (from 7th to 10th week).
- **Group 6(J300):** was given 10% fructose solution and *Nardostachys jatamansi* extract (J300) 300 mg/kg/d by oral gavage (from 7th to 10th week).
- **Group 7(DA):** was given 10% fructose solution and amlodipine (AM10) 10mg/kg/d by oral gavage (from 7th to 10th weeks).

Body weight and SBP was measured for all rats weekly. SBP was measured by a tail-cuff method using the NIBP System (Panlab). Normal systolic blood pressure (SBP) in rats is 84-134 mmHg. [24] SBP ≥135 mmHg was taken as the cut-off for hypertension.

Statistical analysis:

Mean ± Standard Deviation (SD) was calculated from the data collected. Statistical analysis was done using Analysis of Variance (ANOVA) test followed by Tukey's post-hoc analysis.

RESULTS

Table 1: SBP of groups 2,3,4,5,6, and 7 as compared to the control group (1) at the end of week 6

Group	Onset of hypertension (Week)	SBP±SD (mmHg)	p Value (vs. Group 1 with SBP = 98±15)
2 (D)	6	147±7	<0.001*
3 (DR8)	6	149±7	<0.001*
4 (DR25)	6	153±8	<0.001*
5 (J200)	6	143±9	<0.001*
6 (J300)	6	147±8	<0.001*
7 (DA)	6	139±3	<0.001*

Table 1 shows that hypertension (SBP ≥135 mmHg) developed in all groups at the end of week 6.

Table 2: Significant decrease in SBP in groups 3,4,5,6 and 7 when compared to group 2

Group	Week	SBP (Mean±SD) in mmHg	p Value vs. Group 2 (Disease)	SBP (Mean±SD) of group 2 in that week in mmHg
3 (DR8)	9	134±10	0.001*	160±7
4 (DR25)	8	133±11	0.013*	156±11
5 (J200)	9	137±10	0.005*	160±7
6 (J300)	8	135±6	0.036*	156±11
7 (DA)	8	120±11	<0.001*	156±11

Table 2 shows that a significant decrease in SBP was achieved in group 3 and 5 in 9th week; and in groups 4, 6 and 7 in 8th week; with statistically significant difference ($p<0.05$) in all the groups when compared to group 2 (disease) indicating a significant reduction in SBP when compared to group 2.

Table 3: SBP of Treatment groups (3,4,5 and 6) Vs. group 7 (Standard drug) at the end of 10 weeks

Group	SBP (Mean±SD) in mmHg	p Value vs. Group 7 (103±14 mmHg)
3 (DR8)	129±12	0.023*
4 (DR25)	112±14	0.900
5 (J200)	118±7	0.413
6 (J300)	107±10	0.997

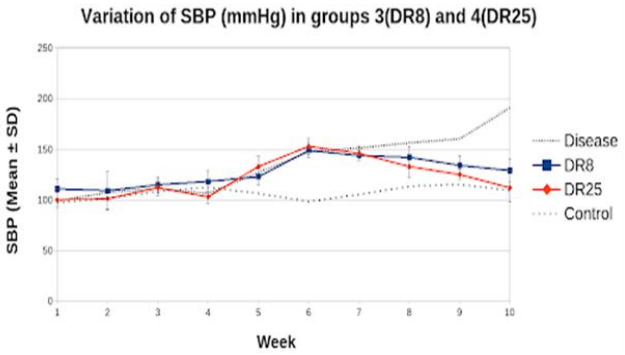
Table 3 shows that the SBP of groups 4,5 and 6 did not differ significantly from the standard drug Amlodipine (group 7) at the end of 10 weeks indicating comparable efficacy of drotaverine (25 mg/kg) and Jatamansi (200 and 300 mg/kg) to the standard drug Amlodipine.

* $p < 0.05$ (Statistically significant)

Table 4: Comparison of drotaverine and *Nardostachys jatamansi* at the end of 10 weeks

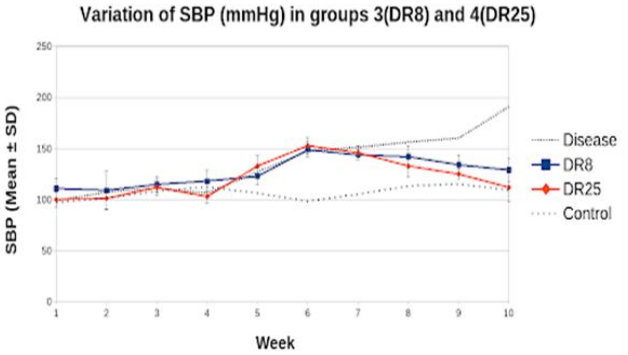
p Value Vs.	J200 (group 5)	J300 (group 6)
DR8 (group 3)	0.791	0.093
DR25 (group 4)	0.976	0.997

Table 4 shows the comparison between two doses of Drotaverine (8 and 25 mg/kg) and *Nardostachys jatamansi* (200 and 300 mg/kg) at the end of 10 weeks. At the end of 10 weeks, SBP of groups 3, 4, 5 and 6 are not significantly different from each other ($p>0.05$) indicating a comparable effect of Drotaverine and *Nardostachys jatamansi* on SBP.



Graph 1: Variation of SBP in groups 3 and 4

Drotaverine was administered in 2 doses, 8 mg/kg (Group 3/DR8) and 25 mg/kg (Group 4/DR25), from week 7 to week 10. Variation of SBP in both the groups is shown in Graph 4.SBP decreases from week 7 to week 10 in both the groups DR8 and DR25. Decrease of SBP in DR25 is more than DR8.



Graph 2: Variation of SBP in groups 5 and 6

Nardostachys jatamansi was administered in 2 doses, 200 mg/kg (Group 5/J200) and 300 mg/kg (Group 6/J300), from week 7 to week 10. Variation of SBP in both the groups is shown in Graph 5. SBP decreases from week 7 to week 10 in both the groups J200 and J300. Decrease of SBP in J300 is more than J200.

DISCUSSION

Rats in Group 1 (C) were given RO-water for 10 weeks. Hypertension did not develop in this group. In all other groups, drinking water was replaced with 10% fructose solution. Hypertension developed in the 6th week in all the groups (2,3,4,5,6 and 7). (Table 1)

In group 2 (D) hypertension was sustained till the end of the study (10th week) as no treatment was given. Continuous decline in SBP is seen among all the treatment groups (3,4,5 and 6) and standard drug (group 7) from week 7 to week 10. (Graph 1,2)

In group 3 (DR8) SBP was significantly decreased in week 9 ($p = 0.001$) and in group 4 (DR25) SBP was significantly decreased in week 8 ($p = 0.013$). At the end of 10 weeks the SBP of group 3 (DR8) was 129±12 mmHg and of group 4 (DR25) was 112±14 mmHg. Thus, significant decrease in SBP is achieved earlier in group 4 (week 8) as compared to group 3 (week 9). Moreover, DR25 lowered the value of SBP more as compared to DR8 at the end of 10 weeks. This could be because of the higher dose used in group 4 (DR25) showing a dose dependent activity of drotaverine in lowering the blood pressure. But the difference of SBP among both the groups is not statistically significant with a p-value of 0.747 in week 8, 0.760 in week 9 and 0.284 in week 10. (Table 1,2 and Graph 1,2)

Therefore, in the present study the effect of the two doses of drotaverine is not significantly different from each other. Further studies of longer duration are needed to explore whether the two different doses of drotaverine produce significantly different results or not. The underlying mechanism behind the lowering of SBP by drotaverine could be the blockade of L-type calcium channels leading to vasodilation as reported by Zsuzsanna Tömösközi, Olivier Finance, et. al. and Zoltán Patai, András Guttman, et. al. [15,25]

In group 5 (J200) SBP was significantly decreased in week 9 ($p = 0.005$) and in group 6 (J300) SBP was significantly decreased in week 8 ($p = 0.036$). At the end of 10 weeks the SBP of group 5 (J200) was 118±7 mmHg and of group 6(J300) was 107±10 mmHg. Thus, significant decrease in SBP is achieved earlier in group 6 (week 8) as compared to group 5 (week 9). Moreover, J300 lowered the value of SBP more as compared to J200 at the end of 10 weeks. This could be because of the higher dose used in group 6 (300 mg/kg) as compared to group 5(200 mg/kg), showing a dose-dependent activity of *Nardostachys jatamansi* in lowering the blood pressure. But the difference of SBP among both the groups is not statistically significant with a p value of 0.142 in week 9 and 0.779 in week 10. (Table 1,2 and Graph 1,2)

Therefore, in the present study the effect of the two doses of *Nardostachys jatamansi* is not significantly different from each other. Further studies of longer duration are needed to explore whether the two different doses of *Nardostachys jatamansi* produce significantly different results or not. The underlying mechanism behind the lowering of SBP by *Nardostachys jatamansi* could be (-)-aristolone and kanshone H induced vasodilation via activation of PDK1-Akt-eNOS-NO relaxing pathway and stimulation of the opening of the K_{ATP} channel as reported by Jingmei Fang, Ran Li, et. al. or due to ACE inhibitor activity as reported by Biswajit Bose, Debabrata Tripathy et. al. and Foroogh Namjoyan, Mohammad Ebrahim Azemi, et. al. [26-28]

In group 7(DA) SBP was significantly lowered at week 8 (SBP = 120±11 mmHg) which is in accordance with the previous studies done by Bernobich Elena, Cosenzi Alessandro, et. al. and T. Anila, A. Sudheer, et. al. [29-30]

At the end of 10 weeks, SBP of none of the treatment groups (3,4,5 and 6) was significantly different from the control group (1). On the other hand, the SBP of all the treated groups was significantly different from the disease group (2). Thus, significant decrease in SBP is achieved in all the treated groups. (Table 3)

At the end of 10 weeks, SBP of none of the treatment groups (3,4,5 and 6) was significantly different from the standard drug amlodipine (group 7). Thus, it could be concluded that the level of control of hypertension achieved in treatment groups is comparable to the standard drug amlodipine. (Table 3)

At the end of 10 weeks, SBP of drotaverine groups (DR8, DR25) and Jatamansi groups (J200, J300) did not differ significantly from each other. Thus, it could be concluded that both drotaverine and Jatamansi had similar efficacy in the present experiment. (Table 4)

Thus, the present study shows that both drotaverine and *Nardostachys jatamansi* are having antihypertensive properties. However, additional research needs to be conducted in a greater number of animal models in order to further confirm these results. Moreover, safety of drotaverine and *Nardostachys jatamansi* as compared to Amlodipine needs to be assessed.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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